American College of Radiology
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ADJUVANT THERAPY FOR RESECTED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Summary of Literature Review

Introduction

The standard definitive treatment of locoregionally advanced squamous cell cancer of the head and neck (SCCHN) is either concurrent chemoradiotherapy (CRT) or appropriate surgical resection followed by adjuvant therapy directed by pathologic risk factors. However, local or regional recurrences and distant metastases remain frequent after surgical treatment of stage III or IV disease [1,2]. Radiation therapy (RT) is added to surgery to decrease locoregional failure. Adjuvant RT has been shown to improve locoregional control compared to neoadjuvant RT in a multi-institutional randomized trial [3].

Postoperative RT (PORT) has traditionally been given for most patients with potentially resectable stages III, IVa, and IVb SCCHN with the goal of maximizing cure and maintaining organ function. Following PORT, locoregional control is 69%-72%, and 5-year survival rates approach 30%-40% [4,5]. This has prompted interest in adding chemotherapy to surgery and RT to improve outcome. The addition of concurrent chemotherapy to adjuvant RT has been shown to result in improved locoregional control, disease-free survival (DFS), and/or overall survival (OS) rates for selected SCCHN patients.

Role of Postoperative Radiation Therapy

The addition of PORT became an accepted treatment following the publication of results from the MD Anderson Cancer Center (MDACC) which demonstrated that adjuvant RT decreased recurrence [3,6]. The Radiation Therapy Oncology Group® (RTOG®) 73-03 trial randomized 320 (T2-T4, N any) head and neck cancer patients to 50 Gy preoperatively versus 60 Gy postoperatively. The 10-year locoregional control was significantly improved in the postoperatively treated patients (70% vs 58%). OS was not different between the groups due to deaths from distant metastases and second primary cancers [3]. Further evidence supporting the role of adjuvant RT includes an analysis by the Surveillance, Epidemiology and End Results (SEER) program of node-positive head and neck cancer patients reporting an absolute 10% overall and cause-specific survival benefit at 5 years [7]. All nodal stages and primary sites (except oral cavity) had improved 5-year OS rates following PORT compared to patients who did not receive PORT [8]. Additionally, within a randomized study of postoperative patients, a prospective cohort of nonrandomized low-pathologic-risk postoperative patients was observed. Compared to patients with intermediate pathologic risk treated with PORT, the low-risk group had *comparable, if not worse* locoregional control [9]. Finally, a small randomized study of buccal mucosa patients demonstrated a DFS benefit to PORT compared to surgical resection alone [10].

While many studies [4,5,9,11] have attempted to establish pathologic risk groups to justify the level of treatment intensity, PORT is generally indicated in patients with higher-risk features for locoregional recurrence after surgery. These include advanced T stage (T3/T4), the presence of lymphovascular invasion, the presence of perineural invasion, positive surgical margins, lymph node involvement, extracapsular nodal extension, and bone involvement.

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High-risk pathologic features were initially defined by two large analyses. A post-hoc analysis of a randomized study of SCCHN patients treated at MDACC demonstrated that extranodal extension was an independent predictor of recurrence, and that two or more involved lymph nodes trended toward worse locoregional recurrence. These factors were validated in a combined analysis of postoperative RTOG[®] studies. RTOG[®] 85-03 testing the addition of cisplatin prior to PORT and RTOG[®] 88-24 [12] testing the addition of concurrent cisplatin to PORT were reanalyzed to determine the importance of different pathologic features on risk of recurrence. Patients treated on RTOG[®] 85-03 were stratified into three post-hoc groups. Group 1 included those with no more than two pathologically involved lymph nodes, no extracapsular spread (ECS), and uninvolved surgical margins; group 2 included patients with two or more pathologically involved lymph nodes or extranodal extension and surgically uninvolved margins; and group 3 included patients with microscopically involved surgical margins. These risk stratifications resulted in significant differences in 5-year locoregional recurrence rates, 17%, 27%, and 67% in groups 1 2, and 3, respectively. Furthermore, median survival times were different among the three groups, being 5.6 years in group 1, 2.6 years in group 2, and 1.5 years in group 3. (See Variant 1.)

Timing of PORT

When PORT is delivered without chemotherapy, the combination of surgical resection and PORT should be considered as a treatment package. Completion of the treatment package in as short a time as possible has been associated with improved locoregional control and survival rates, which are likely related to tumor repopulation effects. The strongest evidence favoring completion of surgery and PORT within a tight schedule comes from a trial at the MDACC randomizing 213 patients to a tailored therapy based on their respective risk factors: patients with no pathologic risk features received no PORT; those in the intermediate-risk group (n = 31) received 57.6 Gy over 6.5 weeks; and those in the high-risk group were randomized to receive either 63 Gy over 5 weeks (n = 76) or 7 weeks (n = 75). For high-risk patients, completion of the entire treatment package in <11 weeks was associated with improved actuarial 5-year locoregional control (76%) compared to packages of 11-13 weeks duration (62%) and >13 weeks duration (38%) (P=0.002) [9]. Although a statistically significant OS benefit defined as a P value <0.05 was not seen, patients receiving accelerated PORT over 5 weeks trended towards improved survival (P=0.08) and locoregional control (P=0.11). Some single institution retrospective analyses support this finding while others do not [13,14]. Confounding these analyses is the fact that potentially larger tumors with high-risk features required larger more complex operations with potentially longer recovery times, which may influence the initiation of PORT.

When PORT is delivered with concurrent chemotherapy, the impact of time to completion of treatment is presently unknown. In general, the treatment should be completed in as short a time frame as possible when patients have adequately healed from their surgical wounds. However, when the RTOG[®] examined the addition of postoperative paclitaxel followed by radiation concurrent with paclitaxel and cisplatin, there was a noted improvement in locoregional control rates and survival when compared to historical controls [15]. Therefore, whether the timing of PORT affects outcomes in the setting of concurrent chemotherapy is not clear.

Role of Concurrent Chemoradiotherapy Postoperatively

The European Organization Research and Treatment of Cancer (EORTC) study 22931 and RTOG[®] 95-01 both examined whether the addition of cisplatin (100 mg/m^2) to 60-66 Gy PORT would improve outcomes for SCCHN patients who had undergone macroscopically complete resections. The trials differed in their inclusion criteria defining high-risk populations. While both trials included patients with involved surgical margins (EORTC: within 5 mm of the specimen edge; RTOG[®]: microscopically involved mucosal margins of resection) and extranodal spread, the RTOG[®] study also included patients with multiple pathologically involved lymph nodes. The EORTC study did not include patients strictly on the basis of multiple pathologically involved lymph nodes, but did include patients with T3-T4 primaries, those with perineural or lymphovascular invasion, and oral cavity primary patients with level IV or V nodal metastasis. Furthermore, the primary endpoint of the RTOG[®] study was locoregional control, compared to progression-free survival (PFS) in the EORTC study [5,16].

The RTOG[®] study demonstrated improved 3-year locoregional progression rates (22% vs 33%, P=0.01), improved DFS rates (47% vs 36%, P=0.04) and a trend towards improved OS rates (56% vs 47%, P=0.09) with the addition of concurrent chemotherapy. However, the updated 5-year results demonstrated that locoregional control (79.5% vs 71.3%, P=0.086) and DFS rates (37.4% vs 29.1%, P=0.098) were only trending toward improvement with the addition of adjuvant cisplatin [5]. In the EORTC study, with a median follow-up of 5 years, adjuvant concurrent cisplatin and RT was associated with a significantly better 5-year PFS rates (47% vs 36%, P=0.04) as well as OS rates (53% vs 40%, P=0.02), a lower rate of locoregional recurrence (18% vs 31%,

P=0.007), and a significantly longer time to disease progression (55 vs 23 months, P=0.02). The incidence of acute severe mucosal toxicity was significantly greater in the cisplatin/RT group (41% vs 21%). In both studies, cisplatin did not influence the rate of distant metastases (EORTC: 25% RT only vs 21% combined, P=0.61; RTOG[®]: 23% RT only vs 21% combined, P=0.46).

A pooled analysis of the RTOG[®] and EORTC studies was performed to determine which characteristics influenced locoregional control, DFS, PFS, and OS. This analysis showed that patients with extracapsular extension (ECE) and/or microscopically involved surgical margins derived benefits in locoregional control (48% risk reduction), DFS (23% risk reduction), and OS (30% risk reduction) with the addition of cisplatin to adjuvant RT [16]. It also demonstrated a possible benefit from cisplatin added to adjuvant RT in patients with stage III-IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. However, the potential impact of the addition of chemotherapy in these individual patient subgroups could not be discerned, since all patients with these risk factors were aggregated in the analysis. Patients who had two or more pathologically involved lymph nodes without ECE as their only risk factor did not seem to benefit from the addition of chemotherapy in this analysis. The lack of significance in any of these categories or any inclusion criteria of the individual studies is not considered to be definitive as neither study was powered to detect such a difference for these subcategories. Additional investigation is needed in larger trials to answer these questions more definitively [16]. (See Variant 2.)

Margin Status

Even though the presence of close or involved margins is associated with increased local recurrence and mortality, the definition of what constitutes a positive margin is not well standardized. At issue is whether a positive margin should reflect cancer at the surgical cut edge or whether it should be considered positive within a specific distance from the cut edge.

Postsurgical margins are most commonly classified in accordance with reporting guidelines from the Royal College of Pathologists [17]. The margin is "negative" if invasive tumor is more than 5 mm from the closest surgical margin, "close" if invasive tumor is within 1 to 5 mm from the surgical margin, and "positive" if invasive tumor is <1 mm from the surgical margin. While the clinical margin may differ on frozen section or due to specimen shrinkage during postsurgical tumor processing [18], it is the final pathologic examination that determines margin status. Furthermore, even a negative margin may be considered unfavorable if there are widely dispersed islands of tumor cells at the margin. Deep margins and surface mucosal margins are reported separately due to their potentially different clinical implications [17].

While a general consensus can be said to exist around these definitions, the critical prognostic and clinical implications associated with margin status have led to some alternative proposals [19-21]. A few authorities have proposed a cutoff of 1-2 mm for close margin status on the basis of better inter-rater reproducibility, and they associate the worst prognosis of positive margins only with cases of tumor cut-through [22]. Others have proposed that clinical margins as large as 2 cm may be necessary in certain clinical scenarios [23]. A recent member survey by the American Head and Neck Society revealed a considerable degree of variation in margin definitions among surgical specialists, with a buffer distance of 5 mm the most commonly used definition [21]. There may be different prognostic implications for margin status based on anatomic location, histologic subtype, tumor thickness, presence of dysplasia, or molecular characteristics [24].

Complicating this issue are technical issues of how the surgical specimen should best be oriented for evaluation and the impact of tissue contraction artificially causing to a closer margin. (See Variant 3.)

The Role of Brachytherapy

Brachytherapy has been used postoperatively in highly selected patients most often with positive margins. Small single institution series at experienced centers report good local control (70%-93%) with brachytherapy alone or in combination with external beam radiotherapy [25-27]. Complications including ulceration, edema, and soft tissue necrosis are more likely to occur in large treatment volumes, higher dose rates, and combination external beam and brachytherapy. The routine use of brachytherapy is unclear in the postoperative setting as the use of brachytherapy was not included in the randomized studies investigating the role of adjuvant chemoradiotherapy [4,5,16,28,29]. (See Variant 4.)

Alternative Agents and Schedules of Systemic Therapy

The most widely accepted concurrent chemotherapy regimen with PORT is cisplatin 100 mg/m^2 on days 1, 22, and 43 of PORT. Due to the significant toxicity associated with the addition of cisplatin 100 mg/m^2, alternative dosing schedules and agents are sought. The use of 50 mg weekly cisplatin concurrently with PORT in patients with stage III/IV disease and extranodal extension resulted in a 23% absolute improvement in OS rates (36% vs 13%, P<0.01), an absolute 15% improvement in locoregional control (70% vs 55%, P=0.05), and a 22% improvement in DFS rates (45% vs 23%, P<0.02) compared to PORT alone [28]. Additionally, the Arbeitsgemeinschaft Radiologishe Onkologie (ARO) 96-3 study demonstrated that multiagent chemotherapy (cisplatin 20 mg/m^2 and 5 fluorouracil (5-FU) 600 mg/m^2 (d1-5 and d29-33) with daily fractionated RT to 66 Gy resulted in statistically significant improvements (compared to PORT alone) in 5-year locoregional control (88.6% vs 72.2%, P=0.00259), and PFS (62.4% vs 50.1%, P=0.024), as well as a 10% absolute improvement in OS rates (58.1% vs 48.6%, P=0.11) that was not statistically significant [29]. No randomized trials have been performed comparing different dosing schedules of cisplatin concurrent with PORT, despite the use of alternative schedules, including 30-40 mg/m^2 weekly cisplatin.

Alternative agents tested with PORT include carboplatin. Two randomized studies have attempted to determine if the addition of carboplatin to PORT would improve outcomes compared to PORT alone. However, both studies were terminated early, one due to poor accrual, and the other when the preliminary results of EORTC 22931 were released. In both of these studies, 100 mg/m^2 carboplatin was administered either in single weekly or twice weekly doses. Neither of these studies showed a benefit in locoregional control, DFS, or OS with the addition of carboplatin to PORT. It remains unknown if this outcome was due to inactivity or small sample size.

No randomized data exist on the use of other agents, such as taxanes. Therefore, the use of cytotoxic agents other than cisplatin-containing regimens cannot be recommended outside the confines of a clinical trial.

There are no randomized data to support the routine use of cetuximab, a humanized monoclonal antibody to the epidermal growth factor receptor (EGFR) ligand binding domain, adjuvantly following resection for SCCHN. Therefore, the use of cetuximab in the postoperative setting should be limited to clinical trials. The combination of cetuximab and radiotherapy is currently being studied by the RTOG® (0920) for patients with intermediate pathologic risk features. (See Variant 5.)

PORT Doses and Treatment Volumes

Few dose finding studies have been conducted when PORT is given alone or with concurrent chemotherapy. When PORT is given as the sole adjuvant therapy, sequential studies led by MDACC have attempted to identify the appropriate PORT dose. The first of these studies divided postoperative head and neck cancer patients into high-risk and low-risk groups based on various pathologic risk factors. Subsequently, low-risk patients were randomized to 52.2-54 Gy, 57.6 Gy, or 63 Gy. High-risk patients were randomized to 63 Gy or 68.4 Gy at the primary or pathologically involved neck. Surgically undisturbed sites (contralateral neck) received 54 Gy, and 57.6 were given to dissected but pathologically uninvolved regions. Low-risk patients were noted to have improved control with doses >57.6 Gy. High-risk patients however, had improved control when treated to 63 Gy but not higher doses. When patients treated to the same dose were compared, there was no difference in locoregional progression based on risk stratification. Post-hoc analyses determined that ECE was identified as the most important pathologic risk factor risk factor, as patients with ECE treated to 63 Gy had a 2-year locoregional control of 74% compared to 52% in patients treated to 57.6 Gy. Although other groupings of risk factors were considered to be associated with worse prognosis, including four or more risk factors (not ECE) and more than one node involved with cancer, none of them reached statistical significance. The conclusions of this study were that patients with ECE benefitted from doses to the involved nodal regions to 63 Gy, and that for all other patients, there was no benefit from doses above 57.6 Gy [11].

To improve control in high-risk populations of postoperative patients, the integration of alternative fractionation schedules has been attempted. A multi-institutional study investigated the use of altered fractionation radiation (63 Gy in 5 weeks or 63 Gy in 7 weeks) for patients with high-risk features [9]. Although not statistically significant, patients who received the accelerated treatment regimen trended towards improvements in locoregional control (P=0.11) and OS rate (P=0.08).

When PORT is given concurrently with chemotherapy, doses of 60-66 Gy in 2 Gy daily fractions to high-risk areas (primary tumor bed with positive margin, or nodal regions with ECS) are common. Doses of 50-54 Gy in 2 Gy fractions are usually given to areas at risk for microscopic involvement. No randomized study has established

the optimal dose of PORT to be given in concurrently with cisplatin-based therapy. There is little evidence supporting the higher PORT doses used in these randomized trials over those recommended from the PORT-alone dose-finding studies. In three of four randomized studies testing the utility of chemotherapy concurrently with PORT, doses >65 Gy were delivered to high-risk areas [4,28,29]. The fourth study, RTOG® 95-01 allowed a dose of 60 Gy with or without an optional 6 Gy boost. As these studies were associated with significant benefits for patients with ECE and positive margins, we recommend similar dosing schedules.

The typical treatment volume used in PORT for head and neck cancer includes the bilateral neck as well as the surgically dissected primary tumor site. However, it is unclear whether both the neck and primary always need to be within the PORT volume. For patients with completely resected primary tumors whose sole indication for PORT is pathologic cervical adenopathy, some would direct therapy only to the neck. Additionally for patients with a positive margin as the sole indication for treatment in the setting of a comprehensive neck surgery, some would direct treatment to the primary resection bed only. Additionally for well-lateralized oral cavity and primary tumors, patterns of progression would suggest that PORT to the ipsilateral neck only may be appropriate. For PORT treatment, patients are usually immobilized in customized devices to ensure reproducible setup. For radiotherapy planning, preoperative imaging and operative findings are used to define the areas of highest risk, and preoperative imaging is often fused to the treatment planning CT scan. There are no randomized comparisons of 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT) in the postoperative setting. In general, IMRT is routinely used to ensure adequate target coverage and spare salivary glands from radiation exposure. However, care must be taken to avoid geographic misses, as out-of-target recurrences have been seen in the spared parotid gland of the contralateral neck. (See Variant 6.)

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

References

1. Johnson JT, Barnes EL, Myers EN, Schramm VL, Jr., Borochovitz D, Sigler BA. The extracapsular spread of tumors in cervical node metastasis. *Arch Otolaryngol.* 1981;107(12):725-729.
2. Snow GB, Annyas AA, van Slooten EA, Bartelink H, Hart AA. Prognostic factors of neck node metastasis. *Clin Otolaryngol Allied Sci.* 1982;7(3):185-192.
3. Tupchong L, Scott CB, Blitzer PH, et al. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. *Int J Radiat Oncol Biol Phys.* 1991;20(1):21-28.
4. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.
5. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
6. Maccomb WS, Fletcher GH. Planned combination of surgery and radiation in treatment of advanced primary head and neck cancers. *Am J Roentgenol Radium Ther Nucl Med.* 1957;77(3):397-414.
7. Lavaf A, Genden EM, Cesaretti JA, Packer S, Kao J. Adjuvant radiotherapy improves overall survival for patients with lymph node-positive head and neck squamous cell carcinoma. *Cancer.* 2008;112(3):535-543.
8. Kao J, Lavaf A, Teng MS, Huang D, Genden EM. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. *Int J Radiat Oncol Biol Phys.* 2008;71(2):362-370.
9. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;51(3):571-578.
10. Mishra RC, Singh DN, Mishra TK. Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. *Eur J Surg Oncol.* 1996;22(5):502-504.
11. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys.* 1993;26(1):3-11.
12. Cooper JS, Pajak TF, Forastiere A, et al. Precisely defining high-risk operable head and neck tumors based on rtog #85-03 and #88-24: Targets for postoperative radiochemotherapy? *Head & Neck.* 1998;20(7):588-594.

13. Schiff PB, Harrison LB, Strong EW, et al. Impact of the time interval between surgery and postoperative radiation therapy on locoregional control in advanced head and neck cancer. *J Surg Oncol.* 1990;43(4):203-208.
14. Vikram B, Strong EW, Shah J, Spiro RH. Elective postoperative radiation therapy in stages III and IV epidermoid carcinoma of the head and neck. *Am J Surg.* 1980;140(4):580-584.
15. Rosenthal DI, Harris J, Forastiere AA, et al. Early postoperative paclitaxel followed by paclitaxel and cisplatin concurrent with radiation therapy (RT) (phase II trial RTOG H-0024) is well tolerated for patients with resected, high-risk squamous carcinoma of the head and neck (HNSCC). *International journal of radiation oncology, biology, physics.* 2004;60(1):S322.
16. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck.* 2005;27(10):843-850.
17. Woolgar JA, Triantafyllou A. A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection specimens. *Oral Oncol.* 2005;41(10):1034-1043.
18. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. *Head Neck.* 1997;19(4):281-286.
19. Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. *Int J Radiat Oncol Biol Phys.* 1989;16(1):25-36.
20. Looser KG, Shah JP, Strong EW. The significance of "positive" margins in surgically resected epidermoid carcinomas. *Head Neck Surg.* 1978;1(2):107-111.
21. Meier JD, Oliver DA, Varvares MA. Surgical margin determination in head and neck oncology: current clinical practice. The results of an International American Head and Neck Society Member Survey. *Head Neck.* 2005;27(11):952-958.
22. Sawair FA, Irwin CR, Gordon DJ, Leonard AG, Stephenson M, Napier SS. Invasive front grading: reliability and usefulness in the management of oral squamous cell carcinoma. *J Oral Pathol Med.* 2003;32(1):1-9.
23. Harrison D. The questionable value of total glossectomy. *Head Neck Surg.* 1983;6(2):632-638.
24. Batsakis JG. Surgical excision margins: a pathologist's perspective. *Adv Anat Pathol.* 1999;6(3):140-148.
25. Chao KS, Emami B, Akhileswaran R, Simpson J, Spector G, Sessions D. The impact of surgical margin status and use of an interstitial implant on T1, T2 oral tongue cancers after surgery. *Int J Radiat Oncol Biol Phys.* 1996;36(5):1039-1043.
26. Beitler JJ, Smith RV, Silver CE, et al. Close or positive margins after surgical resection for the head and neck cancer patient: the addition of brachytherapy improves local control. *Int J Radiat Oncol Biol Phys.* 1998;40(2):313-317.
27. Fujita M, Hirokawa Y, Kashiwado K, et al. Interstitial brachytherapy for stage I and II squamous cell carcinoma of the oral tongue: factors influencing local control and soft tissue complications. *Int J Radiat Oncol Biol Phys.* 1999;44(4):767-775.
28. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys.* 1996;36(5):999-1004.
29. Fietkau R, Lautenschlager C, Sauer R, et al. Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: Results of the German phase III trial ARO 96-3. *J Clin Oncol (Meeting Abstracts).* 2006;24(18_suppl):5507.\

Clinical Condition: **Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck**

Variant 1: **60-year-old man with pT2N2b base of tongue (BOT) squamous cell carcinoma, status post transoral laser excision and ipsilateral neck dissection. Pathologic review of the specimen revealed that three lymph nodes were involved with metastatic cancer; however, surgical margins were negative. There was no ECS, lymphovascular invasion, or other adverse pathologic risk features.**

Treatment	Rating	Comments
PORT to 57-60 Gy	7	
PORT to 63-66 Gy	5	
No adjuvant therapy	1	
PORT to 60-66 Gy with systemic therapy	No Consensus	Consensus could not be reached on the addition of chemotherapy concurrently with PORT for this patient scenario. Ongoing investigations will help to clarify the role of concurrent PORT and systemic therapy.
Radiation Therapy Volume		
Ipsilateral neck irradiation plus primary	2	
Bilateral neck irradiation plus primary	8	
Ipsilateral neck irradiation only	1	
Primary tumor bed irradiation only	1	
Adjuvant brachytherapy without EBRT	1	
Adjuvant brachytherapy with EBRT	1	
Choice of Systemic Therapy if Administered		
Cisplatin (100 mg/m^2) x 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) x 3 cycles	5	
Cisplatin weekly (<30 mg/m^2)	1	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	3	
Cetuximab weekly	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck**

Variant 2: **68-year-old man with pT4N1 squamous cell carcinoma of the pyriform sinus, status post laryngopharyngectomy and bilateral neck dissection. Examination of the surgical specimen reveals no extracapsular spread, no involved surgical margins, and no other high-risk features.**

Treatment	Rating	Comments
PORT to 57-60 Gy	8	
PORT to 63-66 Gy	7	
PORT to 60-66 Gy with systemic therapy	5	
No adjuvant therapy	2	
Radiation Therapy Volume		
Ipsilateral neck irradiation plus primary	3	
Bilateral neck irradiation plus primary	8	
Ipsilateral neck irradiation only	1	
Primary tumor bed irradiation only	1	
Adjuvant brachytherapy without EBRT	1	
Adjuvant brachytherapy with EBRT	1	
Choice of Systemic Therapy if Administered		
Cisplatin (100 mg/m^2) x 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) x 3 cycles	5	
Cisplatin weekly (<30 mg/m^2)	1	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	3	
Cetuximab weekly	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck**

Variant 3: **65-year-old man with pT3N2a squamous cell carcinoma of the retromolar trigone following segmental mandibulectomy and ipsilateral neck dissection. The surgical margin is involved, no other adverse pathologic risk factors are present, and no further resection is offered.**

Treatment	Rating	Comments
PORT to 60-66 Gy with systemic therapy	9	
PORT to 63-66 Gy	3	
PORT to 57-60 Gy	2	
No adjuvant therapy	1	
Radiation Therapy Volume		
Ipsilateral neck irradiation plus primary	3	
Bilateral neck irradiation plus primary	8	
Ipsilateral neck irradiation only	1	
Primary tumor bed irradiation only	1	
Adjuvant brachytherapy without EBRT	1	
Adjuvant brachytherapy with EBRT	1	
Choice of Systemic Therapy if Administered		
Cisplatin (100 mg/m^2) x 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) x 3 cycles	5	
Cisplatin weekly (<30 mg/m^2)	1	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	3	
Cetuximab weekly	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck**

Variant 4: **55-year-old woman with pT2N1 oral tongue cancer following wide local excision and ipsilateral neck disection. Margins are negative, but lymphovascular invasion was identified. The positive lymph node was located ipsilaterally at level 3.**

Treatment	Rating	Comments
PORT to 57-60 Gy	8	
PORT to 63-66 Gy	6	
PORT to 60-66 Gy with systemic therapy	3	
No adjuvant therapy	3	
Radiation Therapy Volume		Some panel members recommended treatment of the ipsilateral neck and primary tumor bed only, if the primary tumor was superficial and well lateralized.
Ipsilateral neck irradiation plus primary	6	
Bilateral neck irradiation plus primary	8	
Ipsilateral neck irradiation only	2	
Primary tumor bed irradiation only	2	
Adjuvant brachytherapy without EBRT	1	
Adjuvant brachytherapy with EBRT	1	
Choice of Systemic Therapy if Administered		
Cisplatin (100 mg/m^2) x 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) x 3 cycles	5	
Cisplatin weekly (<30 mg/m^2)	1	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	3	
Cetuximab weekly	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck**

Variant 5: **72-year-old man has a pT2N2b SCC of the soft palate following wide local excision and bilateral neck dissection. Pathologic evaluation of the specimen reveals ECS but no positive margins. He is ECOG = 0 and has a long-standing creatinine level of 1.7.**

Treatment	Rating	Comments
PORT to 60-66 Gy with systemic therapy	9	
PORT to 63-66 Gy	5	
PORT to 57-60 Gy	2	
No adjuvant therapy	1	
Radiation Therapy Volume		
Ipsilateral neck irradiation plus primary	1	
Bilateral neck irradiation plus primary	8	
Ipsilateral neck irradiation only	1	
Primary tumor bed irradiation only	1	
Adjuvant brachytherapy without EBRT	1	
Adjuvant brachytherapy with EBRT	1	
Choice of Systemic Therapy if Administered		
Cisplatin (100 mg/m^2) x 2 to 3 cycles	3	
Cisplatin (75 mg/m^2) x 3 cycles	3	
Cisplatin weekly (<30 mg/m^2)	2	
Cisplatin weekly ($\geq$30 mg/m^2)	3	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	7	
Cetuximab weekly	5	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck**

Variant 6: **60-year-old man with pT1N1 squamous cell carcinoma of the tonsil status post wide local excision and ipsilateral selective neck dissection. Evaluation of the pathologic specimen reveals no extension to the palate or tongue. Surgical margins are negative, and there is no extranodal extension present. There are no other adverse pathologic features present.**

Treatment	Rating	Comments
No adjuvant therapy	8	
PORT to 57-60 Gy	2	
PORT to 63-66 Gy	1	
PORT to 60-66 Gy with systemic therapy	1	
Radiation Therapy Volume		
Ipsilateral neck irradiation plus primary	2	
Bilateral neck irradiation plus primary	1	
Ipsilateral neck irradiation only	1	
Primary tumor bed irradiation only	1	
Adjuvant brachytherapy without EBRT	1	
Adjuvant brachytherapy with EBRT	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		